Conclusions of the RSNN Expert Meeting: Regulatory challenges for non-biological complex drugs (NBCDs) (8 December 2020)

The RSNN expert meeting on 8 December 2020 discussed and elaborated potential research questions on the theme of 'Regulatory challenges for complex generic products'. Fourteen experts were invited in a personal capacity to discuss this theme in an informal setting. The diverse list of participants included regulatory experts, clinical experts, academic professionals and representatives of the innovative and generic industries.

New therapeutic modalities are becoming more and more complex and make increasing use of so-called nanotechnology. Many of these complex products are referred to as 'Non-Biological Complex Drugs' (NBCDs), which are similar in complexity to biologics. We now see generic versions of some of these synthetic complex products coming to the market. During this RSNN expert meeting, participants were invited to discuss this complexity and the associated challenges for medicine developers, regulators and clinical practitioners. The meeting was held under the Chatham House Rule. This report contains a brief summary of that discussion and the regulatory science questions identified by the organisers of this expert meeting are also listed.

1. THE ROLE AND IMPORTANCE OF SCIENTIFIC ADVICE

Like biological medicinal products ('biologics'), NBCDs are complex drugs that may contain heterogeneous mixtures of related components that cannot be isolated, fully quantified or characterised with existing analytical methods. As with biologics, the manufacturing process is the determining factor for the exact composition and quality of the product. Due to the

complexity of NBCDs, the manufacturing process of NBCD follow-on products involves many challenges.

Scientific advice therefore plays an important role when submitting applications for complex generic products such as NBCD follow-ons. For example, both national scientific advice and European scientific advice can be provided upon request of a pharmaceutical company to establish which clinical and pre-clinical data are required for a successful application. National consultations usually involve live meetings and provide a quick and easy way to interact with regulators. This process creates a quicker way to obtain answers, which could expedite the development process. However, the requisite knowledge of complex generic products is not always readily available at the national level. In these cases, advice is obtained from the EMA's Scientific Advice Working Party (SAWP), which can slow down the development process.

NBCD follow-on products present a challenge because they are very complex products that can require more complex clinical trials compared to 'simple' small-molecule generics. With the increasing complexity, there is also an increasing likelihood of disparities between the scientific advice provided. Any scientific advice requested from the EMA, however, is always assured of Europe-wide backing. During the expert meeting, it became clear that this could be another reason for generic product developers to approach the EMA directly for advice. However, there are also drawbacks to this, namely that the EMA normally provides scientific advice in writing, it is more expensive and takes longer to process.

The expert meeting discussed whether it would be desirable to make more use of the combined expertise in the Member States that the EMA has at its disposal. This could be used by the EMA's SAWP to provide broadly supported and more focused scientific advice on complex generics. European guidance on the proper authorisation procedure could possibly facilitate this. A more central role for the EMA could also contribute to greater harmonisation of the scientific advice provided within Member States. During the expert meeting, however, it was indicated that assessors from different Member States regularly

meet each other in various European working groups, which already provides opportunities for sharing experiences and best practices. Nevertheless, a central system for scientific advice supported at the European level could save time for generic product developers seeking scientific advice. Together with a central role for the EMA, this could also contribute to more harmonisation at the global level. Other regulatory authorities (e.g. the U.S. Food and Drug Administration, FDA) could then be in direct contact with the EMA for the coordination of scientific advice for specific products/product classes. This could build on existing initiatives, such as internal discussions in the Coordination Group for Mutual Recognition and Decentralised Procedure (CMDh), which is already proactively looking into which drugs (including 'complex' drugs) are close to the expiry of their market exclusivity period and for which there could be potential challenges for generic product developers. For some of these products, the Pharmacokinetic Working Party of the EMA is already developing product-specific guidances.

Research questions

- How often is scientific advice obtained at the national and European level for applications for NBCD follow-on products? When is this advice not obtained and what are the reasons for this?
- Do NBCD follow-on products for which prior scientific advice has been obtained have higher success rates for marketing authorisations?
- How much time and money do generic product developers spend on average when applying for national scientific advice as opposed to European scientific advice? In how many cases do questions remain unanswered?
- What general challenges do regulators and medicine developers of NBCD follow-on products face that can be addressed through scientific advice? Could guidance/reflection documents (as used in the past with biosimilars) be of help here?

2. WHAT IS THE CORRECT AUTHORISATION PROCEDURE: 10(1) OR 10(3)?

The appropriate marketing authorisation procedure must be absolutely clear for effective planning of the generic product development process. There are two authorisation procedures in Europe that can be followed to approve (complex) generics: a generic application according to Article 10(1) (i.e. the traditional generic procedure) or a hybrid application according to Article 10(3). Following the 10(1) or the 10(3) route has strategic and economic consequences for generic product developers. In some EU countries, approval through the 10(1) or 10(3) route has an impact on the use of the product in clinical practice. For example, in some countries the conditions for product substitution in clinical practice can be depended on the authorisation procedure that has been used.

Also, differences between the 10(1) and 10(3) route are not always clear and Member States can therefore disagree about which authorisation procedure is most appropriate in certain situations. In principle, it is not possible to submit additional clinical data through a 10(1) application alongside one or more bioequivalence studies. The requirements for a 10(3) application, on the other hand, can range from fairly small dossiers with a simple bioequivalence study and literature references, to very extensive applications with a comprehensive clinical study. In some cases, for example if a formulation differs slightly and one or more comparative bioavailability studies are sufficient, a product may be approved in a 10(1) procedure where it formally requires a 10(3) application. This can sometimes result in different countries applying different procedures.

Pharmaceutical companies developing complex generics are faced with uncertainties due to the fragmentation of the expertise held within the European Member States, the various challenges involved in obtaining authorisations for individual complex products or complex product classes and, in some cases, a lack of agreement on whether to follow the 10(1) or 10(3) route. This may contribute to disparate decisions and outcomes in authorisation procedures. It is therefore important that generic product developers receive timely information on which authorisation procedure is appropriate for their product and that they are clearly informed about the expectations of regulators in the decision-making process. In addition to more centralised and clearer scientific advice on the requirements for individual

products or product classes (see previous theme), it would also help if regulators and generic product developers interacted early in the application process. A so-called early dialogue between reviewers and generic product developers (similar to an FDA pre-ANDA meeting) could help to remove some of the uncertainty in the development process and make the assessment process more efficient. In the EU, the product-specific guidances of the EMA are used for this purpose. Scientific advice can also be requested at an early stage by generic firms, which may make NBCD follow-on products more readily available to patients.

Research questions

- What are the important differences between a 10(1) and a 10(3) application? Can 10(1) and 10(3) applications be compared to identify any significant differences or similarities?
- How do 10(1) and 10(3) applications for NBCD follow-on products translate into successfully approvals and use in clinical practice?
- What are the main bottlenecks that result in unsuccessful applications for NBCD follow-on products? What are common reasons for rejection?
- Is there a better way to identify best practices and the reasons for unsuccessful applications? Is it possible to share these experiences with the community through publications so that the process can be made more transparent and efficient?
- Can the European system learn from the experiences of other regulatory authorities such as the FDA?

3. OTHER IMPORTANT ASPECTS

The participants in the expert meeting discussed a number of other important facets of NBCD follow-on products. First, the so-called critical quality attributes (CQAs) were mentioned. CQAs can provide more insight into the production process and the development of complex generics that are safe, effective and of high quality. Critical process parameters (CPPs), Q1/Q2 sameness and so-called process signatures also play an important role here. With more insight into the impact of these factors on NBCD products, the

development processes for NBCD follow-on products can be made more efficient and predictable.

It can also help to develop product-specific guidances for NBCD products or product classes, as has been done in the past for biosimilars. Currently, the CMDh and the EMA both facilitate this process at the central level. The desired guidances for generic products can be developed in consultation with the various Member States, as in the case of liposomal doxorubicin, for example. The aforementioned identification of CQAs, CPPs, etc. could also play an important role in some cases. The participants also referred to the existing EMA reflection papers on nanomedicines, which paint a fairly holistic picture and thus leave room for different interpretations. Furthermore, the potential for new manufacturing issues in the development process of NBCD follow-on products may require adjustments to existing guidance. It is therefore important to keep product-specific guidances up to date and at the same time communicate any changes to generic developers clearly and as quick as possible.

Another challenge that came up during the expert meeting was the role of pharmacovigilance in NBCD products. Because NBCD products face similar challenges as biologics, it would be desirable to have a centralised pharmacovigilance process. As with biosimilars, for NBCD follow-on products such as glatiramoids or iron products, it is important to be able to identify possible differences in the safety and efficacy profiles of products from different manufacturers. Because NBCD products are not of 'biological' origin, these products do not fall under the European pharmacovigilance legislation for biologics and are therefore currently not required to be identifiable by brand name and batch number in reports of adverse reactions.

Finally, this expert meeting indicated that it is important to look at the challenges of NBCD follow-on products from a 'patient-oriented view'. In other words, what are the implications for the patient? When is a product sufficiently 'clinically equivalent'? What are acceptable risks for the patient? What should generic product developers consider when demonstrating clinical equivalence? Which endpoints are important for the patient? What

studies can increase the confidence of prescribers? How can education and the provision of reliable information increase confidence in, and the appropriate use of, NBCD follow-on products?

Research questions

- To what extent are NBCD (follow-on) products from different manufacturers currently traceable and therefore 'distinguishable' in adverse drug reaction (ADR) reports?
- Are there clinical issues with NBCD/NBCD follow-on products that may currently go unnoticed and could be better identified?
- What problems have been encountered with NBCD products in clinical practice? Are there any issues related to their use in clinical practice?
- How can a 'patient-oriented view' be incorporated into the development process of NBCD follow-on products?

The RSNN will incorporate the results of this meeting in future research agendas to inform policy discussions.